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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/254,529	08/04/1999	SUSAN MARY KINGSMAN	9192.9USWO	7151

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THOMAS J. KOWALSKI, ESQ.
FROMMER LAWRENCE & HAUG LLP
745 FIFTH AVENUE
NEW YORK, NY 10151

EXAMINER	
KAUSHAL, SUMESH	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/254,529	KINGSMAN ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,26,28-30,33,34,36-38 and 40-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☒ Claim(s) *24, 26, 28-30, 33-34, 36-38 and 40-43* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/09/04 has been entered.

Claims 24, 26-34, 36-38 and 40-43 are pending and are examined in this office action.

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **571-273-8300**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 24, 26, 28-30, 33-34, 36-38 and 40-43 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lisziewicz (WO92/21750, 1992, ref of record), Hope et al (PNAS, 87:7787-7791, 1990, ref of record) and Riviere et al (US

6544771, 2003) for the same reasons of record as set forth in the office action mailed on 06/10/04.

The scope of the instant claims encompasses a retroviral vector or a DNA construct encoding a packageable RNA genome for a retroviral vector particle, wherein the retroviral vector particle, when in the form of a DNA provirus, comprises: (i) a 5'LTR comprising an HIV U3 and R region having Tat inducible promoter activity (ii) at least one retroviral polynucleotide response element (PRE) which is responsive to a nucleus to cytoplasm transport factor, wherein the PRE is a retroviral Rev response element (RRE); wherein the PRE is located within an intron in a transcription unit of the provirus, wherein the intron is flanked by a retroviral splice donor (SD) site and a retroviral splice acceptor (SA) site derived from different retroviruses, wherein the construct comprises an insertion site within the intron containing the PRE at which one or more nucleotide sequences (NS) may be inserted; and wherein the construct is operably linked to a promoter.

Regarding claims 24, 26-30, 33-34, 36-38 and 40-41 Liziewicz teaches a retroviral vector (MLV) incorporating HIV Rev/RRE system, wherein the RRE is located within the transcriptional unit of the foreign gene or within the transcriptional unit of the vector (page 6, line 21-32 page 9, line 1-4 and fig. 1-4). Liziewicz further teaches that the vector contain an internal promoters operably linked to the foreign gene and DNA sequence encoding the RRE (page 9, line 5-26). The cited art teaches that RRE can be inserted in the vector in the LTR, in front of the foreign gene, behind the foreign gene or within an intron of the foreign gene (page 9, line 5-11). Regarding claim 24(i), 34(i), and 37(i) The cited art teaches that the preferred LTRs include the MLV LTRs or HIV LTRs (page 8, line 5). The retroviral vector (MLV) as taught by Liziewicz include a strong promoter (HIV LTR) which is switched on in the presence of the virus or viral-transactivator protein (**tat**), but in the absence of viral infection does not express the encoded gene product (page 12, line 14-25 and fig-4, page 13, line 19-24). Therefore, Liziewicz clearly teaches a retroviral vector wherein the nucleotide sequence of interest is located within an intron in the transcription unit of a provirus and the gene expression is only limited to HIV infected cells in the presence of tat.

Regarding claims 24, 34 and 37 Hope et al teaches that HIV-1 transactivator Rev is a nuclear protein that regulates the expression of HIV transcripts by binding to the Rev response elements (RRE) present in the HIV transcripts. Hope et al further teaches a retroviral vector comprising splice donor sequence, RRE and splice acceptor sequences, wherein the gene of interest (CAT) is located within the splice donor and splice acceptor sites (page 7787, abstract; page 7788, fig-1). Furthermore, the transcripts produced by this vector harbor a single intron, which contain CAT coding sequences (page 778, col.1. Para.1). Regarding claims 40-41 the cited art further teaches the infection of MT4 cells with recombinant viral particles in vitro (page 21 col.2 para.2).

Even though the combined teaching of Liziewicz and Hope suggest a tat/rev responsive retroviral vector the cited does not teach splice donor (SD) and splice acceptor (SA) sites derived from different retroviral vectors that flanks the provirus intron and gene of interest.

Regarding claims 24, 34, 37 and 42-43 Riviere teaches a recombinant retroviral vector containing splice donor and splice acceptor cites obtained from different retroviruses. The cited art teaches a recombinant retroviral vector useful to transfect cells, comprising: (i) a 5' LTR derived from a retrovirus of interest; (ii) a splice donor site located 3' to said 5' LTR; (iii) a Psi packaging site located 3' to said splice donor site; (iv) a consensus splice acceptor site, located 3' to said Psi packaging site; (v) an insertion site for a gene of interest located 3' to said consensus splice acceptor site; and (vi) a 3' LTR derived from a retrovirus of interest located 3' to said insertion site (Col. 28, lines 44-57; Col. 29, lines 15-30, Col. 30 lines 50-65). Given the broadest reasonable interpretation the cited art clearly anticipate a retroviral vector comprising splice donor and splice acceptor sites derived from different retroviruses.

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the retroviral vector (MLV) as taught by Liziewicz, by incorporating a nucleotides of interest within the splice acceptor site (HIV) as taught by Hope et al. One would have been motivated to do so because the insertion of a RRE (HIV) into the intron of foreign gene and within splice donor and splice acceptor sites provides the

regulation of the expression of a foreign gene by RRE element which is only switched on in the presence REV protein. It would have been further obvious to modify the combined teaching of Liziewicz and Hope by substituting splice donor and splice acceptor sites derived from different retroviruses. One would have been motivated to incorporate HIV splice acceptor site to conserve the functionally of HIV RRE in the construct. One would have a reasonable expectation of success because the regulation of HIV LTR by Tat-protein and RRE by Rev-protein has been a well characterize phenomenon in the art at the time the instant invention was made. In addition making a retroviral vector containing splice donor and splice acceptor sites derived from different retroviruses is well within the reach of one ordinary skill in the art, since art at the time of filing clearly teaches that even consensus sequence comprising a splice donor and splice acceptor sites are capable of producing spliced transcripts. Thus the invention as claimed is prima facie obvious in view of the prior art of record.

Response to arguments

The applicant argues that there is no teaching in any of the references that renders the claimed invention obvious. Lisziewicz, Hope or Riviere, alone or in combination, do not teach a Tat- and Rev inducible retroviral vector, where there is no basal transcription in the absence of Tat and Rev. The applicant argues that on the other hand, the claimed invention achieves a Rev-dependent intron by the placement of splice sites that flank an RRE-containing intron, and by the splice sites being derived from different retroviruses. The applicant argues that neither Lisziewicz, Hope or Riviere teach, suggest or provide a motivation to make a retroviral vector having splice sites derived from a different retrovirus. The applicant argues that there is not teaching in any of cited references that suggest or provide motivation to effect inefficient splicing within a retroviral vector. The applicant argues that Riviere does not teach the use of SD and AS sites that are derived from different retrovirus. The applicant argues that Riviere teaches a retroviral vector wherein both sites are derived from a MLV based retrovirus.

However, applicant's arguments are found NOT persuasive. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law (**See MPEP 2144**).

In this case, Liziewicz teaches a retroviral vector (MLV) incorporating HIV Rev/RRE system, wherein the RRE is located within the transcriptional unit of the foreign gene or within the transcriptional unit of the vector. The retroviral vector (MLV) as taught by Liziewicz include a strong promoter (HIV LTR) which is switched on in the presence of the virus or viral-transactivator protein (**tat**), but in the absence of viral infection does not express the encoded gene product. Therefore, Liziewicz clearly teaches a retroviral vector wherein the nucleotide sequence of interest is located within an intron in the transcription unit of a provirus and the gene expression is only limited to HIV infected cells in the presence of tat. Hope teaches a retroviral vector comprising splice donor sequence, RRE and splice acceptor sequences, wherein the gene of interest (CAT) is located within the splice donor and splice acceptor sites (page 7787, abstract; page 7788, fig-1). The transcripts produced by this vector harbor a single intron, which contain CAT coding sequences (page 778, col.1. Para.1). Therefore the combined teaching of Liziewicz and Hope clearly teaches a tat/rev responsive retroviral vector comprising splice donor (SD) and splice acceptor (SA) sites. However Liziewicz and Hope does not teach that the splice donor (SD) and splice acceptor (SA) sites are derived from different retroviral vectors that flanks the provirus intron and gene of interest.

This modification could have been easily made in view of Riviere who teaches a recombinant retroviral vector containing splice donor and splice acceptor cites obtained from different retroviruses comprising: (i) a 5' LTR derived from a retrovirus of interest; (ii) a splice donor site located 3' to said 5' LTR; (iii) a Psi packaging site located 3' to said splice donor site; (iv) a consensus splice acceptor site, located 3' to said Psi packaging site; (v) an insertion site for a gene of interest located 3' to said consensus splice acceptor site; and (vi) a 3' LTR derived from a retrovirus of interest located 3' to said insertion site (Col. 28, lines 44-57; Col. 29, lines 15-30, Col. 30 lines 50-65). A consensus splice acceptor site is inherently different from the native splice acceptor site of a retrovirus. Therefore Riviere clearly teaches that the splice donor site and the splice acceptor cite are obtained from different retrovirus. In addition the scope of Riviere's invention is not limited to MLV-based vector but encompasses any retroviral vector containing a splice donor sited obtained from a retrovirus of interest and consensus splice acceptor site (see col. 28, lines 14-57). Therefore combination of a slice acceptor site and consensus splice acceptor site as disclosed by Riviere clearly reads upon a splice acceptor and splice donor sites, which are not derived from same retrovirus.

Thus it would have been obvious to one ordinary skill in the art at the time of filing to modify the retroviral vector (MLV) as taught by Liziewicz, by incorporating a nucleotides of interest within the splice acceptor site (HIV) as taught by Hope. One would have been motivated to do so because the insertion of a RRE (HIV) into the intron of foreign gene and within splice donor and splice acceptor sites provides the regulation of the expression of a foreign gene by RRE element which is only switched on in the presence REV protein. It would have been further obvious to modify the combined teaching of Liziewicz and Hope by substituting splice donor and splice acceptor sites derived from different retroviruses. One would have been motivated to incorporate HIV splice acceptor site to conserve the functionally of HIV RRE in the construct. One would have a reasonable expectation of success because the regulation of HIV LTR by Tat-protein and RRE by Rev-protein has been a well characterize phenomenon in the art at the time the instant invention was made. In addition making a retroviral vector containing splice donor and splice acceptor sites derived from different

retroviruses is well within the reach of one ordinary skill in the art, since art at the time of filing clearly teaches that even consensus sequence comprising a splice donor and splice acceptor sites are capable of producing spliced transcripts. Thus the invention as claimed is prima facie obvious in view of the prior art of record.

Conclusion

No claims are allowed.

This is a *continuation* of applicant's earlier Application No. 09/254,529. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to **571-272-0547.** For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Sumesh Kaushal
Examiner GAU 1636

JEFFREY FREDMAN
PRIMARY EXAMINER
1/26/05